JC02 Rec'd PCT/PTO 25 MAR 2002

Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
		P32422
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/089013
INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09442	21 September 2000	25 September 1999
TITLE OF INVENTION		
PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS		
APPLICANT(S) FOR DO/EO/US		
Howard MARSHALL, Mervyn THOMPSON, and Paul Adrian WYMAN		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/EP00/09442, filed 21 September 2000, which claims benefit from the following Provisional Applications: GB 9922831.4 filed 25 September 1999; GB 0001936.4 filed 27 January 2000; and GB 0013873.5 filed 07 June 2000.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (if known see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
10/089013	PCT/EP00/09442	P32422

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,040.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**16 - 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**2 - 3 =**	**0**	**0 x $84.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$890.00**	
				Amount to be refunded	**$**
				charged	**$890.00**

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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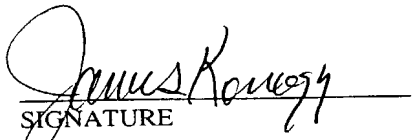

SIGNATURE
James M. Kanagy
NAME
29,550
REGISTRATION NO.

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PATENT
ATTORNEY'S DOCKET NUMBER **P32422**

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE
(DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09442	21 September 2000	25 September 1999

TITLE OF INVENTION
PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS

APPLICANT(S) FOR DO/US
Howard MARSHALL, Mervyn THOMPSON, and Paul Adrian WYMAN

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

In the Claims:

Please amend the following claims:

4. A compound according to claim 1 in which Y is CH_2.

6. A compound according to claim 1 in which W is $-CH_2-CH_2-$ or -CH=CH-.

7. A compound according to claim 1 in which R^c is hydrogen or methyl.

8. A compound according to claim 1 in which R^d and R^e are both methyl.

12. A compound according to claim 1 for use in therapy.

13. A compound according to claim 1 for use in the treatment of depression.

14. A pharmaceutical composition which comprises a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

15. A compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT_{1B} receptor is beneficial.

16. The use of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT_{1B} receptor is beneficial.

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/EP00/09442 in the §371 national phase of prosecution.

A marked version of the amended claims accompanies this paper.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

James Kanagy

James M. Kanagy
Attorney for Applicant
Registration No. 29,550

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n:\jmk\patapps\P51027\prelimamend.doc

MARKED UP VERSION OF CLAIMS TO SHOW CHANGES MADE

4. A compound according to ~~any of the preceding claims~~claim 1 in which Y is CH_2.

6. A compound according to ~~any of the preceding claim~~claim 1 in which W is $-CH_2-CH_2-$ or -CH=CH-.

7. A compound according to ~~any of the preceding claims~~claim 1 in which R^c is hydrogen or methyl.

8. A compound according to ~~any of the preceding claims~~claim 1 in which R^d and R^e are both methyl.

12. A compound according to ~~any one of claims 1 to 10~~claim 1 for use in therapy.

13. A compound according to ~~any one of claims 1 to 10~~claim 1 for use in the treatment of depression.

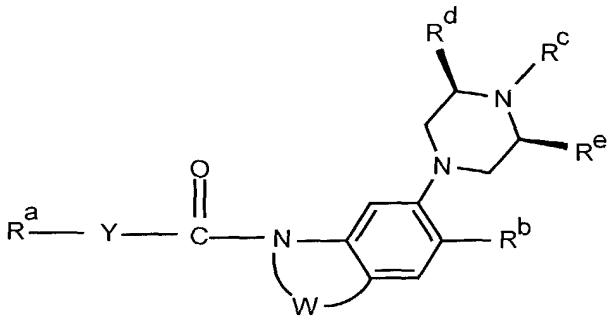
14. A pharmaceutical composition which comprises a compound according to ~~any of claims 1 to 10~~claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

15. A compound of formula (I) as defined in ~~any one of claims 1 to 10~~claim 1 or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of the $5\text{-}HT_{1B}$ receptor is beneficial.

16. The use of a compound of formula (I) as defined in ~~any one of claims 1 to 10~~claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of the $5\text{-}HT_{1B}$ receptor is beneficial.

ABSTRACT

Novel piperazine derivatives of formula I



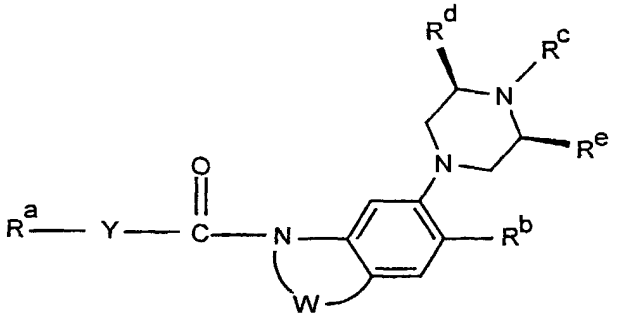
processes for their preparation, and pharmaceutical compositions containing them are provided herein.

PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS

The present invention relates to novel piperazine derivatives, processes for their preparation, pharmaceutical compositions containing the same and to their use in the treatment of CNS and other disorders.

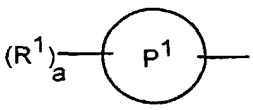
WO 95/06637 discloses a series of piperazine derivatives which are said to possess 5-HT_{1D} receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. The human 5-HT_{1D} receptor is now known to be encoded by two distinct genes initially designated 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ and subsequently redesignated as 5-HT_{1D} and 5-HT_{1B} respectively (P.R. Hartig et al, Trends in Pharmacological Science, 1996, **17**, 103 - 105). WO 98/50538 and WO 98/47885 disclose a series of piperazine derivatives that are said to exhibit combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist activity. WO 98/27058 discloses a series of carboxamide derivatives that are claimed to be 5-HT_6 receptor antagonists.

A structurally novel class of compounds has now been found which also exhibit 5-HT_{1B} receptor activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which R^a is a group of formula (i)



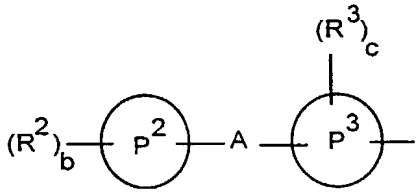
(i)

wherein P^1 is phenyl, naphthyl or heteroaryl;

R^1 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, nitro, CF_3, cyano, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, CO_2R^6, $CONR^6R^7$, $OCONR^6R^7$, NR^6R^7, $NR^6CO_2R^7$, $NR^6CONR^7R^8$, $CR^6{=}NOR^7$ where R^6, R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;

a is 0, 1, 2 or 3;

or R^a is a group of formula (ii)



(ii)

wherein

P^2 is phenyl, naphthyl, heteroaryl or a 5 to 7 membered heterocyclic ring;

P^3 is phenyl, naphthyl or heteroaryl;

A is a bond or oxygen, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;

R^2 is as defined above for R^1 in formula (i) or R^2 is heteroaryl optionally substituted by C_{1-6}alkyl, halogen or COC_{1-6}alkyl or is a 5 - 7 membered heterocyclic ring optionally substituted by oxo;

R^3 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^6, $CONR^6R^7$, NR^6R^7 where R^6 and R^7 are as defined above;

b and c are independently 0, 1, 2 or 3;

Y is a single bond, CH_2, O or NR^5 where R^5 is hydrogen or C_{1-6}alkyl;

W is $-(CR^9R^{10})_t-$ where t is 2, 3 or 4 and R^9 and R^{10} are independently hydrogen or C_{1-6}alkyl or W is a group CH=CH;

R^b is hydrogen, halogen, hydroxy, C_{1-6}alkyl, CF_3 , COC_{1-6}alkyl, cyano or C_{1-6}alkoxy;

R^c is hydrogen or C_{1-6}alkyl;

R^d and R^e are independently C_{1-4}alkyl.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

Where used herein the term naphthyl is intended, unless otherwise stated, to denote both naphth-1-yl and naphth-2-yl groups.

The term "heteroaryl" is intended to mean an aromatic or a benzofused aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such benzofused aromatic rings include quinolinyl, isoquinolinyl, indolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl and the like.

The term "5 - 7 membered heterocyclic ring" is used herein to mean a non aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such non aromatic rings include piperidinyl, piperazinyl, pyrrolidinyl and morpholinyl.

The heteroaryl and 5 - 7 membered heterocyclic rings, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Within the definition of R^a formula (i)

When P^1 is heteroaryl a preferred example is pyridyl. Preferably P^1 is phenyl or naphthyl, most preferably phenyl.

When a is other than 0, preferred R^1 groups include halogen (particularly fluoro or chloro), C_{1-6}alkyl group (particularly methyl), CF_3 and cyano. When a is 2 or 3 the groups R^1 can be the same or different.

Preferably a is 1 or 2, most preferably 2.

Within the definition of R^a formula (ii)

Preferably A is a bond.

When P^3 is heteroaryl preferred examples include quinolinyl and pyrazolyl. P^3 is preferably phenyl or naphthyl. A preferred substitution arrangement for such naphthyl groups is 1,4 or 1,5, that is to say, a naphth-1-yl group in which the group A is attached at the 4 or 5 position respectively.

P^2 is preferably phenyl, a heteroaryl group such as pyridyl, pyrazinyl, oxadiazolyl or oxazolyl or P^2 is a 5 – 7 membered heterocycle such as piperidinyl.

When b is other than 0, preferred R^2 groups include halogen (particularly chloro), C_{1-6}alkyl group (particularly methyl), heteroaryl (particularly oxadiazolyl optionally substituted by C_{1-6}alkyl) or a 5 – 7 membered heterocyclic ring (particularly 2-oxo pyrrolidinyl). When b is 2 or 3 the groups R^2 may be the same or different. Preferably b is 0, 1 or 2.

When c is other than 0, preferred R^3 groups are halogen (particularly chloro) and C_{1-6}alkyl group (particularly methyl). When c is 2 or 3 the groups R^3 may be the same or different. Preferably c is 0 or 1.

A preferred group of formula (ii) is that in which A is a single bond, P^2 is pyridyl (particularly 2-pyridyl) and P^3 is naphthyl (particularly naphth-1-yl). A further preferred group of formula (ii) is that in which A is a single bond, P^2 is pyridyl and P^3 is phenyl. Such groups may be optionally substituted by the preferred R^2 and R^3 groups as described above.

Y is preferably a single bond, CH_2 or a NH group.

It will be appreciated that when W is a group -CH=CH- an indole ring is formed. Within the definition of the group W, the groups R^9 and R^{10} are each preferably hydrogen and t is preferably 2 or 3, most preferably 2.

R^b is preferably hydrogen, C_{1-6}alkoxy group (particularly methoxy) or C_{1-6}alkyl group (particularly methyl).

R^c is preferably hydrogen or methyl.

Preferably both R^d and R^e are methyl.

Preferred compounds of this invention are examples E1 - E73 (as described below) or a pharmaceutically acceptable salt thereof. Particularly preferred compounds according to this invention are:

cis-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole,

cis-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,

cis-1-[(2,3-dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline

cis-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl]indoline,

cis-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole,

cis-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indole,

cis-1-[2-chloro-3-(trifluoromethyl)phenyl)aminocarbonyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline

or a pharmaceutically acceptable salts thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

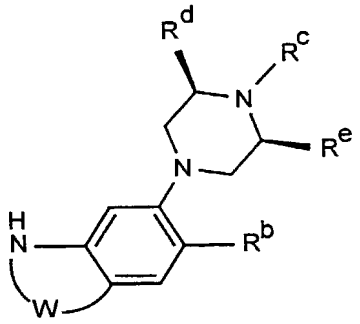
Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises either:

(a) where Y is NH, coupling a compound of formula (II):

$$R^a\text{–N-(C = O)}$$

(II)

in which R^a is as defined in formula (I) with a compound of formula (III):



(III)

in which W, R^b, R^c, R^d and R^e are as defined in formula (I); or

(b) where Y is NR^5, reacting a compound of formula (IV)

$$R^a\text{-}NR^5H$$

(IV)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) as defined above together with an appropriate urea forming agent; or

(c) where Y is a single bond, CH_2 or O, reacting a compound of formula (V)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L$$
(V)

in which R^a is as defined in formula (I) and L is an appropriate leaving group, with a compound of formula (III) as defined above;
and optionally thereafter for either process (a), (b) or (c):

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

The reaction in process (a) is conveniently effected in an organic solvent such as dichloromethane.

In process (b) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (c) the leaving group L may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine. Alternatively L may be an O-benzotriazole group, prepared from hydroxybenzotriazole and a carbodiimide, and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran, dichloromethane or dimethylformamide at ambient or elevated temperature.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. The following examples are given by way of illustration of this point rather than limitation. For compounds of formula (I) wherein R^c is hydrogen, it is possible to introduce a C_{1-6}alkyl group by conventional alkylation using 1 molar equivalent of a C_{1-6}alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. For compounds of formula (I) wherein W is a group $-CH_2CH_2-$, it is possible to convert this to a group wherein W is -CH=CH- with an oxidising agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in an inert solvent such as dichloromethane or toluene.

Intermediate compounds of formula (II), (III), (IV) and (V) are either commercially available or can be prepared using methods described herein, by methods

known to those skilled in the art or by analogous methods thereto. For example, where intermediates of formula (V) are derived from phenylacetic acids, the latter may be prepared from the corresponding benzoic acids by standard homologation methods involving reduction to the benzyl alcohol, followed by conversion to the benzyl bromide, displacement with an inorganic cyanide to afford the benzonitrile, followed by acid or base hydrolysis.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The involvement of serotonin (5-hydroxytryptamine; 5-HT) receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin receptors have been implicated in pharmacological effects such as mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, pain disorders as well as other psychiatric disorders such as schizophrenia and psychosis. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of pre-menstrual tension, sexual dysfunction and hypothermia.

Ligands with high affinity for the 5-HT_1 receptors are well recognised as having therapeutic utility for the treatment of the above conditions. It has been suggested that a

selective 5-HT_{1B} receptor antagonist should act as a fast onset antidepressant (P. Blier Trends Pharmacol. Sci. 1994, 15, 220).

The present invention also provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment of the aforementioned disorders. In particular, the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment or prophylaxis of depression.

In a further aspect the invention provides a method of treating disorders where an antagonist of the 5-HT_{1B} receptor is beneficial, particularly the aforementioned disorders, which comprises administering a safe and therapeutically effective amount of compound of formula (I) or a pharmaceutically acceptable salt to a patient in need thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which an antagonist of the 5-HT_{1B} receptor is beneficial, particularly the aforementioned disorders, more particularly depression.

The affinities of the compounds of this invention for the 5-HT_{1B} receptor can be determined by the following radioligand binding assay. CHO cells expressing 5-HT_{1B} receptors (4×10^7 cells/ml) are homogenised in Tris buffer Mg^{2+} and stored in 1.0 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4nM) in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Tomtec Harvester (filters pre-washed in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

All examples tested in accordance with this radioligand binding assay were found to have a pKi > 7.3 at 5-HT_{1B} receptors with many demonstrating a pKi in the higher range of 8.0 - 9.2.

The selectivity of the compounds of this invention for 5-HT_{1B} receptors can be determined using binding assay methods which are well known to those skilled in the art. All examples tested were found to have a greater than a 10-fold selectivity over 5-HT_{1D} receptors and a greater than 50-fold selectivity over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. Many examples were found to have a greater than a 30-fold selectivity over 5-HT_{1D} receptors and a greater than 80-fold selectivity over other binding sites.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*,

(Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 minutes in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 50 μl of [^{35}S]GTPγS (100pm, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale in which the value 1.0 defines the maximum response elicited by the agonist 5-HT, 0.0 defines antagonism and a negative value indicates inverse agonism. The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display 5-HT_{1B} antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the *in vitro* [^{35}S]GTPγS functional assay are preferred, as these compounds are more likely to be full antagonists *in vivo*. Particularly preferred compounds of this invention have an intrinsic activity in the range 0.0 - 0.3 or are inverse agonists in this functional assay.

It has been found that the compounds of this invention have a particularly advantageous profile in that they demonstrate high affinity and selectivity for the 5-HT_{1B} receptor together with low intrinsic activity in the [^{35}S]GTPγS functional assay.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical

composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-Acetyl-6-bromo-5-methoxyindoline (D1)

A stirred solution of 1-acetyl-6-bromoindolin-5-ol (Tetrahedron 1973, 29(8), 1115; 40g, 0.15mole) in DMF (500ml) was treated with K_2CO_3 (61g, 0.45mole) and iodomethane (11.7ml, 0.19mole) and maintained at room temperature for 20h, then concentrated under vacuum to 200ml. The residue was treated with water (200ml) and the precipitate filtered off, dried and re-crystallised from EtOAc to afford the title compound as a white solid (35.7g, 85%).

Description 2

***cis*-1-Acetyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D2)**

A mixture of palladium (II) acetate (500mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.0g) and cesium carbonate (10.3g) in dry degassed 1,4-dioxane (120ml) under argon was sonicated at 28°C for 0.5h producing a pink heterogeneous mixture. This was treated with D1 (6.0g, 22mmole) followed by *cis*-1,2,6-trimethylpiperazine (J. Med. Chem. 1968, 11, 592; 4.8g, 38mmole) and heated with rapid stirring at reflux for 70h. The mixture was allowed to cool, filtered, then concentrated under vacuum. The residue was treated with water and extracted with EtOAc. The organic solution was then extracted with 1M HCl acid and the aqueous extract was basified by addition of K_2CO_3 and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated under vacuum to leave an orange solid, which was chromatographed on silica gel eluting with 0-10% MeOH/DCM to afford the required product as a pale yellow solid (1.6g, 23%).

Description 3

***cis*-5-Methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D3)**

A stirred solution of D2 (1.6g, 5mmole) in 2M HCl acid (50ml) was heated under reflux for 2h, then the solution was allowed to cool, basified with K_2CO_3 and extracted with DCM. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale orange solid (1.4g, 100%).

Description 4

***cis*-1-Acetyl-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D4)**
The title compound was prepared in 43% yield from *cis*-1-benzyl-2,6-dimethylpiperazine (Org. Prep. Proc. 1976, 8, 19) and D1 using a similar procedure to Description 2.

Description 5
***cis*-6-(4-Benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D5)**
The title compound was prepared from D4 by a similar procedure to Description 3 as a beige solid (100%)

Description 6
***cis*-6-(4-Benzyl-3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]indoline (D6)**
The title compound was prepared from D5 and D13 following a similar procedure to Example 1 as a white solid (85%).

Description 7
Methyl 4-(trimethylstannyl)-1-naphthoate (D7)
A stirred solution of methyl 4-bromo-1-naphthoate (Collect. Czech. Chem. Commun. 1997, 62(11), 1737; 7.3g, 28mmole) in degassed toluene (300ml) was treated with hexamethylditin (10g, 31mmole) and tetrakis(triphenylphosphine)palladium(0) (720mg) and heated at reflux under argon for 3h. On cooling, the mixture was filtered through Celite (Diatomaceous Earth), concentrated under vacuum and the residue chromatographed on silica gel eluting with 0-3% ether/60-80 petrol to afford the title compound as a colourless oil (9.06g, 94%).

Description 8
Methyl 4-(pyridin-4-yl)-1-naphthoate (D8)
A stirred solution of D7 (9.06g, 26mmole) in dry degassed DMF (150ml) was treated with copper (I) iodide (495mg, 2.6mmole), dichlorobis(triphenylphosphine)palladium(II) (1.52g, 2.2mmole) and 4-bromopyridine (prepared by suspending the HCl salt (6.07g, 31mmole) in 40% KOH solution, extracting with toluene and adding the dried toluene solution to the reaction). The mixture was heated at reflux under argon for 5h and allowed to cool before removing the DMF under vacuum. The residue was partitioned between EtOAc and 10% $NaHCO_3$ solution and the organics dried (Na_2SO_4) and chromatographed on silica gel eluting with EtOAc to afford the title compound as a white solid (4.1 g, 60%).

Description 9
Methyl 4-(1-methylpiperidin-4-yl)-1-naphthoate (D9)

A stirred solution of D8 (2.0 g, 7.6 mmole) in acetone (20 ml) was treated with methyl iodide (1.0ml, 15mmole), stirred for 0.5h and then allowed to stand at room temperature for 2 days. The resultant yellow precipitate was filtered off to afford the pyridinium salt as yellow crystals (2.87g). This was dissolved in EtOH (30 ml) and DMF (90 ml) and was hydrogenated at 50 psi (344.8KPa) and room temp over PtO_2 for 24h. The mixture was filtered through Celite (Diatomaceous Earth) and the filtrate concentrated under vacuum to a brown oil. This was partitioned between DCM and 10% $NaHCO_3$ solution and the organic solution separated, dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a brown oil (1.82 g, 91%).

Description 10

Methyl 4-(piperidin-4-yl)-1-naphthoate (D10)

A solution of D9 (0.39g, 1.4mmole) in DCM (30ml) was treated with iPr_2EtN (0.26g, 2mmole) followed by 1-chloroethyl chloroformate (0.29g, 2mmole) and stirred at room temperature for 3h, then concentrated under vacuum and the residue treated with MeOH (30ml) and heated under reflux for 1h. The mixture was allowed to cool and the solid filtered off, washed with Et_2O and dried. This was treated with 10% Na_2CO_3 solution, extracted with DCM and the extract dried and concentrated under vacuum to afford the title compound as a colourless oil (0.33g, 88%).

Description 11

4-(1-*tert*-Butoxycarbonylpiperidin-4-yl)-1-naphthoic acid (D11)

A solution of D10 (0.33g, 1.2mmole) in DCM (30ml) was treated with di-*tert*-butyl dicarbonate (0.28g, 1.25mmole) and stirred at room temperature for 20h, then concentrated under vacuum to leave a white solid (0.44g). This was dissolved in THF (15ml) and MeOH (15ml), treated with LiOH (85mg) in water (10ml) and stirred at room temperature for 20h, then concentrated under vacuum to approx. 10ml. The residue was treated with excess 10% aqueous citric acid and extracted with EtOAc. The extract was dried and concentrated under vacuum to afford the title compound as a white solid (0.41g, 97%).

Description 12

***cis*-1-[4-(1-*tert*-Butoxycarbonylpiperidin-4-yl)-1-naphthoyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D12)**

The title compound was prepared from D11 and D3 using a similar procedure to Example 8 as a pink solid (52%).

Description 13

4-(6-Methylpyridin-2-yl)-1-naphthoic acid (D13)

The title compound was prepared from D7 and 2-bromo-6-methylpyridine using a similar method to Description 8 (45%), followed by hydrolysis of the methyl ester using 1M NaOH solution (69%) to afford a white solid.

Description 14

Methyl 4-(trimethylstannyl)1-naphthylacetate (D14)

The title compound was prepared from methyl 4-bromo-1-naphthylacetate (Zh. Org. Khim. 1966, 2, 1852) using a similar procedure to Description 7 as a colourless oil (69 %).

Description 15

4-(6-Methylpyridin-2-yl)-1-naphthylacetic acid (D15)

The title compound was prepared from D14 and 2-bromo-6-methylpyridine using a similar method to Description 8 (32%), followed by hydrolysis of the methyl ester using 1M NaOH solution (80%) to afford a white solid.

Description 16

4-Formyl-1-naphthylboronic acid (D16)

A mixture of K10 montmorillonite clay (75g) and trimethylorthoformate (75ml) in methanol (75ml) was stirred at room temperature for 0.5h, then filtered. The solid was added to a stirred solution of 4-bromo-1-naphthylcarboxaldehyde (JP 01113354 [1989], 25.70g, 0.11mole) in DCM (300ml). After 18h the mixture was filtered, washed with 20% K_2CO_3 solution (100ml), dried and concentrated *in vacuo* to afford the dimethyl acetal as a yellow oil (29.05g 95%), which was dissolved in anhydrous THF (300ml) at -70°C and treated with a 1.6M solution of n-butyllithium in THF (78ml, 0.12mole). After 1h triisopropyl borate (24.4g, 0.13mole) was added over 0.25h, the mixture stirred for 1h at -70°C then poured into 2M HCl (500ml). The mixture was concentrated to 50% volume *in vacuo*, and extracted with EtOAc. The organic solution was then extracted with 10% NaOH solution (4x50ml) and the combined aqueous solution acidified with 6M HCl and extracted with DCM (3x100ml). The extract was dried and concentrated to dryness *in vacuo* to afford the title compound as a yellow-green powder (13.15g, 64%).

Description 17

4-Carboxy-1-naphthylboronic acid (D17)

To a stirred solution of D16 (0.25g, 1.25mmole) and NaOH (0.15g, 3.75mmole) in water (5ml) at 0°C was added dropwise a solution of $KMnO_4$ (0.19g. 0.120mmole) in water (5ml). After 0.25h sodium metabisulphite (excess) was added and the mixture acidified with 6M HCl and extracted with EtOAc (3x 15ml). The extracts were dried and concentrated to dryness to afford the title compound as cream powder (0.21g, 78%).

Description 18

4-(2,6-Dimethylpyridin-3-yl)-1-naphthoic acid (D18)

A stirred mixture of D17 (0.32g, 1.5 mmole), 3-bromo-2,6-dimethylpyridine hydrochloride (Synthesis 1974, 4, 293; 0.37g, 1.6mmole), Na_2CO_3 (0.48g, 5.6mmole) and tetrakis(triphenylphosphine) palladium (0) (0.08g, 0.07mmole) in 50% DME/water (20ml) was heated at reflux under argon for 18h. The mixture was concentrated *in vacuo* to 50% volume, diluted with water (20ml), washed with EtOAc (2x10ml), acidified with 2M HCl to pH 4 and extracted with DCM (3x25ml). The combined extract was dried and evaporated to dryness. The residue was triturated in Et_2O to afford the title compound as a buff powder (0.29g, 69%).

Description 19

4-(3,6-Dimethylpyrazin-2-yl)-1-naphthoic acid (D19)

The title compound was prepared from D17 and 2-chloro-3,6-dimethylpyrazine using a similar procedure to Description 18 as a cream powder (50%).

Description 20

4-(1-Methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-naphthoic acid (D20)

The title compound was prepared from 3-bromo-1-methyl-6-oxo-1,6-dihydropyridine (Khim.Geterotsikl. soedin. 1982, 12, 1662) and D17 using a similar procedure to Description 18 as a buff powder (78%).

Description 21

***cis*-7-(4-Benzyl-3,5-dimethylpiperazin-1-yl)-6-methoxyquinoline (D21)**

The title compound was prepared from *cis*-1-benzyl-2,6-dimethylpiperazine (Org. Prep. Proc. 1976, 8, 19) and 7-bromo-6-methoxyquinoline (J. Org. Chem. 1990, 55, 2019) using a similar procedure to Description 2 (75%).

Description 22

***cis*-7-(3,5-Dimethylpiperazin-1-yl)-6-methoxy-1,2,3,4-tetrahydroquinoline (D22)**

A solution of D21 (6.8g, 19 mmole) in EtOH (200ml) and THF (200ml) was hydrogenated over 10% Pd-C (1g) at ambient temperature and pressure for 48h, then filtered through Kieselguhr and the filtrate hydrogenated over Pt (1.5g of PtO_2) at ambient temperature and 50psi (344.8Kpa) for 20h. The mixture was filtered through Kieselguhr and the filtrate concentrated under vacuum to afford the title compound as a colourless oil (3.3g, 63%).

Description 23

***cis*-1-Acetyl-7-(3,5-dimethylpiperazin-1-yl)-6-methoxy-1,2,3,4-tetrahydroquinoline (D23)**

A stirred solution of D22 (2.4g, 8.7mmole) in DCM (100ml) at 0°C was treated with acetic anhydride (0.92g, 9mmole) and maintained at 0°C for 6h, then treated with excess 10% Na_2CO_3 solution, stirred for 0.5h, then extracted with DCM. The extract was dried and concentrated under vacuum to afford the title compound as a yellow gum (2.7g, 98%).

Description 24

***cis*-1-Acetyl-6-methoxy-1,2,3,4-tetrahydro-7-(3,4,5-trimethylpiperazin-1-yl)quinoline (D24)**

A stirred solution of D23 (2.7g, 8.5mmole) in MeOH (60ml) at room temperature under Ar was treated with aqueous formaldehyde (3.2ml of 37% w/v, 40mmole), followed by portionwise addition of $NaBH_3CN$ (1.1g, 17mmole). The pH of the mixture was adjusted to 6 by addition of formic acid and stirred at room temperature for 6h, then concentrated under vacuum and the residue treated with 10% Na_2CO_3 solution and extracted with DCM. The extract was dried, concentrated under vacuum and the residue chromatographed on silica gel eluting with 0-20% MeOH/EtOAc to afford the title compound as a yellow solid (1.4g, 50%).

Description 25

***cis*-6-Methoxy-1,2,3,4-tetrahydro-7-(3,4,5-trimethylpiperazin-1-yl)quinoline (D25)**

The title compound was prepared from D24 using a similar procedure to Description 3 as a yellow solid (86%).

Description 26

***cis*-1-Acetyl-6-(4-benzyl-3,5-dimethylpiperazin-1-yl)indoline (D26)**

The title compound was prepared from *cis*-1-benzyl-2,6-dimethylpiperazine (Org. Prep. Proc. 1976, 8, 19) and 1-acetyl-6-bromoindoline (Heterocycles 1987, 26, 2817) using a similar procedure to Description 2 as an off-white solid (53%).

Description 27

***cis*-1-Acetyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D27)**

The title compound was prepared from D26 by hydrogenation over 10% Pd-C using a similar procedure to Example 45, followed by N-methylation using a similar procedure to Description 24 to afford a white solid (59%).

Description 28

***cis*-6-(3,4,5-Trimethylpiperazin-1-yl)indoline (D28)**

The title compound was prepared from D27 using a similar procedure to Description 3 to afford an off-white solid (96%).

Description 29

***cis*-1-Acetyl-5-chloro-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D29)**

A solution of D27 (1.0g, 3.5mmole) in DCM (20 ml) under argon was treated with *N*-chlorosuccinimide (929mg, 7.0mmole) and stirred at room temp. for 3h. The mixture was washed with water, dried and evaporated under vacuum to a buff solid. Column chromatography on silica gel eluting with 5% MeOH/DCM afforded the title compound as a white solid (670mg, 60%).

Description 30

***cis*-5-Chloro-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D30)**

The title compound was prepared from D29 using a similar procedure to Description 3 to afford an off-white solid (72%).

Description 31

***cis*-1-Acetyl-5-bromo-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D31)**

A solution of D27 (884mg, 3.1mmole) in DCM (15 ml) at 0°C under argon was treated with *N*-bromosuccinimide (819mg, 4.6mmole) and stirred at room temp. for 2 days. Additional NBS was added (150mg, 0.84mmole) and stirring continued for 16h. The mixture was washed with 10% Na_2CO_3 solution, dried and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with 5% MeOH/DCM to afford the title compound as a beige solid (440mg, 39%).

Description 32

***cis*-5-Bromo-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D32)**

A solution of D28 (250mg, 1.0mmole) in DCM (40 ml) under argon was treated with trifluoroacetic anhydride (0.15ml, 1.1mmole) and stirred at room temp for 2h. Evaporation *in vacuo* afforded a yellow oil (100%) which was re-dissolved in DCM (10 ml) and treated immediately with *N*-bromosuccinimide (356mg, 2.0 mmole). The mixture was stirred under argon at room temp. for 16h, washed with water, dried and evaporated *in vacuo* to afford a yellow solid (100%), which was dissolved in MeOH (30 ml) and treated under argon with Na_2CO_3 (500mg, 4.7mmole) then stirred at room temperature for 2 days. The mixture was evaporated *in vacuo* and partitioned between water and DCM. The organics were dried and evaporated to afford the title compound as a beige solid (264mg, 80%).

Description 33

***cis*-1-Acetyl-5-ethyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D33)**

A stirred suspension of D31 (200mg, 0.55mmole) in dry DMF (5 ml) was treated with tributyl(vinyl)tin (0.24ml, 0.83mmole) and the mixture degassed by bubbling argon through for 40 minutes. To the mixture was added Et_3N (0.15ml, 1.1 mmole) and tetrakis(triphenylphosphine)palladium (0) (64mg, 0.06mmole) and the mixture heated under argon at reflux for 18h. On cooling, the mixture was diluted with EtOAc (100 ml) and extracted with 0.5M HCl (2x). The aqueous was basified (K_2CO_3), extracted with DCM, dried and evaporated to a buff solid, which was dissolved in EtOH (10 ml) and hydrogenated over 10% Pd/C (20 mg) at room temp. and atmospheric pressure for 2 days. Filtration through Celite (Diatomaceous Earth) and evaporation *in vacuo* afforded the title compound as a buff solid (100 mg, 62%).

Description 34

***cis*-5-Ethyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D34)**

The title compound was prepared from D33 using a similar procedure to Description 3 to afford a buff solid (84%).

Description 35

***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxyindoline (D35)**

The title compound was prepared from D4 by hydrogenation over 10% Pd/C using a similar procedure to Example 45 (98%), followed by hydrolysis in 2M HCl using a similar procedure to Description 3 (80%) to afford the product as a pale brown solid

Description 36

***cis*-1-Acetyl-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D36)**

The title compound was prepared from D31 and tetramethyltin using a similar procedure to Description 33 (20%).

Description 37

***cis*-5-Methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D37)**

The title compound was prepared from D36 using a similar procedure to Description 3 (86%).

Description 38

***cis*-5-Fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D38)**

The title compound was prepared from 1-acetyl-6-bromo-5-fluoroindoline (prepared by bromination of 5-fluoroindoline analogous to procedure in J. Het. Chem. 1983, 20, 349, followed by N-acylation) by reaction with *cis*-3,5-dimethylpiperazine using similar procedure to Description 2 (82%), followed by N-methylation using procedure similar to

Description 24 (69%), followed by hydrolysis as in Description 3 (96%). The product was isolated as a pale yellow solid.

Description 39

N-(4-Acetyl-2-bromophenyl)-N-(2-methylallyl)acetamide (D39)

N-(4-Acetyl-2-bromophenyl)acetamide (25g, 0.1mole) in dry DMF (250ml) was treated with sodium hydride (60%, 4.5g, 0.11mole) at 25°C under argon with stirring for 1h. 3-Bromo-2-methylpropene (11.1ml, 0.11mole) was added and the mixture stirred for a further 16h. The mixture was concentrated *in vacuo* and partitioned between water and Et_2O. The organic phase was dried and concentrated *in vacuo* to give the title compound (32.8g, 100%).

Description 40

1-(5-Acetyl-3,3-dimethylindolin-1-yl)ethanone (D40)

D39 (32.8g, 0.1mole) in toluene (3L) was stirred at 80°C under argon and a solution of tri-*n*-butyltin hydride (40ml) and AIBN (0.9g) in toluene (250ml) added over 25 minutes The mixture was heated at reflux for 4h and concentrated *in vacuo*. The whole was partitioned between EtOAc and aq.K_2CO_3 and the organic phase gave a residue which on trituration with ether gave the title compound as a solid (10.7g, 46%).

Description 41

5-Acetoxy-1-acetyl-3,3-dimethylindoline (D41)

D40 (10.7, 0.05mole) in glacial AcOH (60ml) was stirred at 25°C under argon and a solution of peracetic acid (30%, 22ml, 0.09mole) in AcOH (10ml) added over 30 minutes The mixture was kept at 25°C for 20h, diluted with water (250ml) and extracted with DCM. The organic phase was washed (water, aq.metabisulfite, aq.K_2CO_3) dried (Na_2SO_4) and concentrated to afford the title compound (10.2g, 91%).

Description 42

1-(3,3-Dimethyl-5-hydroxyindolin-1-yl)ethanone (D42)

D41 (10.2, 0.04mole) in MeOH (100ml) and 2M NaOH (52ml) was stirred at 25°C under argon for 4h. Acidification with conc. H_2SO_4 gave a solid which was collected by filtration, washed with water and dried *in vacuo* to give D42 (7.8g, 92%).

Description 43

1-(3,3-Dimethyl-5-methoxyindolin-1-yl)ethanone (D43)

D42 (7.8, 0.04mole) in DMF (100ml) was treated with methyl iodide (4.73ml, 0.08mole), K_2CO_3 (11.1g, 0.08mole) and stirred at 25°C under argon for 24h. The mixture was

diluted with water (500ml) and extracted exhaustively with Et_2O and concentrated to afford the title compound (6.4g, 77%).

Description 44

1-(6-Bromo-3,3-dimethyl-5-methoxyindolin-1-yl)ethanone (D44)

D43 (6.4, 0.03mole) in 2:1DCM:MeOH (420ml) was stirred at 25°C under argon; benzyltrimethylammonium tribromide (13.3g, 0.34mole) was added portionwise and stirring continued for 5h. The mixture was evaporated to dryness and work-up with DCM/ aq.K_2CO_3 afforded the title compound (8.7g, 100%).

Description 45

***cis*-1-Acetyl-3,3-dimethyl-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D45)**

A mixture of palladium (II) acetate (650mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.7g) and cesium carbonate (13.5g) in dry degassed 1,4-dioxane (200ml) under argon was sonicated at 28°C for 0.5h. This was treated with *cis*-2,6-dimethylpiperazine (4.6g, 0.04mole) and D44 (7.4g, 0.025mole) using a method similar to that of Description 2 to give the title compound as a solid (1.6g, 19%).

Description 46

***cis*-3,3-Dimethyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D46)**

D45 was treated with aqueous formaldehyde and sodium cyanoborohydride followed by acid hydrolysis using a procedure similar to that of Descriptions 24 and 3 to give the title compound as a waxy solid. MH^+ 304.

Description 47

4-(2,5-Dimethylpyridin-4-yl)benzoic acid

The title compound was prepared from 4-bromo-2,5-dimethylpyridine (WO 93/15062) and 4-carboxyphenylboronic acid using a similar procedure to Description 18 as a white solid (67%).

Description 48

***cis*-1,5-Diacetyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline**

A solution of D31 (0.75g, 2.0mmole) and (1-ethoxyvinyl)tributyltin (1.08g, 3.0mmole) in dry DMF was treated with tetrakis(triphenylphosphine)palladium(0) (0.12g, 0.10mmole) and triethylamine (0.56ml, 4.0mmole). The mixture was heated to 100°C under argon for 16h. The cooled mixture was diluted with EtOAc (120ml), extracted with 2M HCl (3x 30ml) and the extracts were basified with K_2CO_3 and extracted with DCM (4x30ml). The extracts were dried (Na_2SO_4), concentrated to dryness in vacuum and the residue

was chromatographed on silica gel eluting with 5% MeOH/DCM to afford the crude title compound as a brown oil (0.45g, 67%).

Description 49

***cis*-5-Acetyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline**

A solution of D48 (0.44g, 1.34mmole) in EtOH (5ml) and 2M HCl (5ml) was stirred at room temperature for 5 days. It was then concentrated under vacuum, diluted with water (20 ml), basified with K_2CO_3 and extracted with DCM (3x15ml). The extracts were dried (Na_2SO_4) and concentrated under vacuum. The residue was chromatographed on silica gel eluting with 0-10% MeOH/DCM to afford the title compound as a brown gum (0.21g, 55%).

Example 1

***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E1)**

A suspension of D13 (92mg, 0.35 mmole) in DCM (10ml) was treated with oxalyl chloride (75mg, 0.60mmole) and stirred at room temperature for 18h, then concentrated under vacuum to leave the acid chloride as a yellow solid. This was re-dissolved in DCM (10ml) and added to a stirred solution of D3 (100mg, 0.38mmole) and pyridine (47mg, 0.60mmole) in DCM (10ml) at 0°C under argon. The reaction mixture was allowed to warm to room temperature and stir for 3h, then treated with polystyrene bound methylisocyanate (100mg of 1.2mmole/g) and stirred for 18h, then filtered through Kieselguhr. The filtrate was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4), concentrated under vacuum and the residue purified by chromatography on basic alumina eluting with EtOAc to afford the title compound as a yellow solid (110mg, 60%).

^1H NMR (250MHz, $CDCl_3$) - spectrum highly complex due to hindered rotation with most peaks doubled up. Major peaks discernible: δ 6.75 & 6.68 (2xs, together 1H = 4H), 3.87 & 3.75 (2xs, together 3H = OMe), 3.16 & 3.00 (2xt, together 2H, = indoline CH_2), 2.69 (s, 3H, = pyridyl Me), 2.34 & 2.12 (2xs, together 3H, = piperazine N-Me), 1.17 & 0.85 & 0.79 (3xd, together 6H, = 3 and 5-piperazine Me). MH^+ 521.

Examples E2 - E8 were prepared by a similar method to that of Example 1 using D3 or D25 and an appropriate acid chloride derivative consistent with the final product:

Example	MH^+
***cis*-5-Methoxy-1-[5-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E2)**	521
***cis*-5-Methoxy-1-[5-(2-methyloxazol-5-yl)-1-naphthoyl]-6-(3,4,5-**	511

trimethylpiperazin-1-yl)indoline (E3)	
***cis*-1-(2,3-Dichlorobenzoyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E4)**	448/450
***cis*-5-Methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E5)** (acid ref: EP 0533268A1)	552
***cis*-5-Methoxy-1-[(3-nitrophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E6)**	439
***cis*-6-Methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-1,2,3,4-tetrahydro-7-(3,4,5-trimethylpiperazin-1-yl)quinoline (E7)**	535

Example 8

***cis*-1-[(2-Chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E8)**

A solution of 2-chloro-3-trifluoromethylphenylacetic acid (954 mg, 4.0 mmole) and D28 (950 mg, 3.87 mmole) in DCM (100 ml) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (766 mg, 4.0 mmole) and 1-hydroxybenzotriazole hydrate (612 mg, 4.0 mmole) and stirred at room temp. for 0.5h. The reaction mixture was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale yellow solid (1.15g, 64%).

^1H NMR (250MHz, $CDCl_3$) δ 7.94 (d, 1H), 7.67 (d, 1H), 7.56 (d, 1H), 7.38 (t, 1H), 7.07 (d, 1H), 6.60 (dd, 1H), 4.19 (t, 2H), 3.98 (s, 2H), 3.45 (br d, 2H), 3.17 (m, 2H), 2.53 (t, 2H), 2.34 (m, 2H), 2.22 (s, 3H), 1.13 (d, 6H). MH^+ 466/468.

Example 9

***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E9)**

The title compound was prepared from 2-fluoro-3-trifluoromethylphenylacetic acid (155mg, 0.70mmole) and D3 (150mg, 0.54mmole) using a similar procedure to Example 8. The product was obtained as a pale yellow oil (210mg, 81%), which was converted to its hydrochloride salt as a beige solid.

^1H NMR (free base) (250MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.65-7.50 (m, 2H), 7.25 (t, 1H), 6.72 (s, 1H), 4.17 (t, 2H), 3.84 (s, 3H & s, 2H), 3.35-3.25 (m, 2H), 3.19 (t,2H), 2.55-2.40 (m, 4H), 2.30 (s, 3H), 1.11 (d, 6H). MH^+ 480.

Examples E10 - E43 were prepared by a similar method to that of Example 8 using the appropriate indoline (D3, D28, D30, D32, D34, D35, D37 or D38) and the appropriate carboxylic acid consistent with the final product:

Example	MH^+
***cis*-1-[(2,3-Dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (E10)**	448/450
***cis*-1-[(3-Chloro-2-fluorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E11)**	416/418
***cis*-1-[(2,3-Difluorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E12)**	400
***cis*-1-[(2,3-Dichlorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E13)**	432/434
***cis*-1-[(2-Trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E14)**	432
***cis*-1-[(2,3-Dichlorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E15)**	462/464
***cis*-1-[(2-Trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E16)**	462
***cis*-1-[(3-Chloro-2-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E17)**	446/448
***cis*-1-[(2,3-Difluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E18)**	430
***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylacetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E19)**	535
***cis*-5-Chloro-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E20)**	525/527
***cis*-1-[4-(2,6-Dimethylpyridin-3-yl)-1-naphthoyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E21)** from D18	535
***cis*-1-[4-(3,6-Dimethylpyrazin-2-yl)-1-naphthoyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E22)** from D19	536
***cis*-5-Methoxy-1-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E23)** (from D20)	536
***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E24)**	464
***cis*-1-[(2-Chloro-3-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E25)**	446/448
***cis*-1-[(2-Bromo-3-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E26)**	490/492
***cis*-1-[(2-Bromo-3-chlorophenyl)acetyl]-5-methoxy-6-(3,4,5-**	508/509

trimethylpiperazin-1-yl)indoline (E27)	
***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (E28)**	466
***cis*-1-[(2-Chloro-3-trifluoromethylphenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (E29)**	482/484
***cis*-1-[(3-Chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (E30)**	432/434
***cis*-1-[(2-Chloro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E31)**	496/498
***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E32)**	468
***cis*-1-[(3-Fluoro-2-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E33)**	480
***cis*-1-[(3-Chloro-2-cyanophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E34)**	453/455
***cis*-1-[(2-Acetyl-3-chlorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E35)**	470/472
***cis*-1-[(3-Bromo-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E36)**	486/488
***cis*-1-[(3-Cyano-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E37)**	433
***cis*-5-Bromo-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E38)**	545/546
***cis*-5-Acetyl-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E39)**	508/510
***cis*-5-Methoxy-1-[(2-phenyl-3-(trifluoromethyl)pyrazol-4-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E40)**	514
***cis*-6-(3,5-Dimethylpiperazin-1-yl)-1-[(4-(2,5-dimethylpyridin-4-yl)benzoyl]-5-methoxyindoline (E41)** (from acid D47)	
***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxy-1-[2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl]indoline (E42)** (acid ref: Description 47 in WO 97/34901)	539
***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]indoline (E43)** (acid ref: EP0533268A1)	538

Example 44

***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxy-1-[4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl]-indoline (E44)**

Methyl [4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoate (Description 9 in WO 97/17351) was hydrolysed with 2M NaOH solution to afford the corresponding carboxylic acid, which was coupled with D35 using a similar procedure to Example 8 to afford the title compound. Hydrochloride salt obtained as an off-white solid.
^{1}H NMR (250MHz, $CDCl_3$) δ [rotamers - key signals quoted] 8.00 (br, 1H, indoline), 7.59 & 8.27 (Abq, 2H, J = 8 Hz, pyridyl), 7.40 & 7.62 (Abq, 4H, J = 8 Hz, phenyl), 6.75 (s, 1H, indoline), 3.85 (s, 3H, OMe), 3.10 (t, 2H, J = 8 Hz), 2.68 (t, 2H, J = 8 Hz), 2.47 (s, 3H, pyrMe), 2.14 (m, 2H), 1.13 (br, 6H). MH^+ 540.

Example 45

***cis*-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]indoline (E45)**

A solution of D6 (380mg, 0.64mmole) in EtOH (50ml) and THF (50ml) was treated with 10% Pd-C (300mg) and stirred under a hydrogen atmosphere at ambient temperature and pressure for 70h. The mixture was filtered through Kieselguhr and concentrated under vacuum. The residue was purified by chromatography on basic alumina eluting with EtOAc followed by crystallisation from Et_2O to afford the title compound as a yellow solid (320mg, 98%). MH^+ 507.

Example 46

***cis*-1-[(2-Chloro-3-trifluoromethylphenyl)acetyl]-5-cyano-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E46)**

A stirred mixture of E38 (67mg, 0.12mmole) and copper cyanide (43mg, 0.48mmole) in DMF (2ml) was heated to 130°C for 16h. The cooled mixture was added to conc. aqueous ammonia (50ml), stirred for 30 mins., then extracted with DCM (3x25 ml). The extracts were dried (Na_2SO_4) and concentrated to dryness in vacuum. The residue was dissolved in DCM (2ml) and applied to an SCX resin cartridge (1g) and the resin eluted with DCM (x2), MeOH (x3) and the washings discarded. Final elution with 1M NH_3 in MeOH (x2) afforded the title compound as a pale brown powder (26mg, 43%). MH^+ 491/493.

Example 47

***cis*-1-[(3-Aminocarbonyl-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E47)**

To a stirred suspension of E37 (80mg, 0.19mmole) and K_2CO_3 (26mg, 0.19mmole) in DMSO (1ml) was added dropwise 30% aq. H_2O_2 soln.(0.1ml), then the mixture was warmed to 100 °C for 2 mins. and allowed to cool to room temperature. After 30 mins a

further 0.1 ml of 30% aq. H_2O_2 soln. was added and the mixture again warmed to 100 °C for 2 mins. and allowed to cool. This procedure was repeated twice more, and then the mixture was stirred at room temperature for 16h. It was diluted with water (50 ml) and extracted with DCM (3x20ml), the extracts dried (Na_2SO_4) and concentrated to dryness under vacuum. The residue was triturated in Et_2O to afford the title compound as a cream powder (52mg, 63%). MH^+ 451.

Example 48

***cis*-5-Methoxy-1-[4-(1-methylpiperidin-4-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E48)**

A stirred solution of D3 (58mg, 0.21mmole) in toluene (5ml) under argon was treated with 2M trimethylaluminium in toluene (0.13ml, 0.25mmole), then stirred at room temperature for 0.75h. A solution of D9 (60mg, 0.21mmole) in toluene (5ml) was added and the mixture was heated under reflux for 3.5h, then allowed to cool to room temperature. The mixture was added to a 5g silica gel column and eluted with 0-10% MeOH/DCM to afford a yellow oil. This was further purified by preparative plate TLC on silica gel eluting with 9:1:0.1 DCM/MeOH/0.88 NH_3 to afford the title compound as a white solid (39mg, 35%). MH^+ 527.

Example 49

***cis*-5-Methoxy-1-[4-(piperidin-4-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E49)**

A solution of D12 (45mg, 0.074mmole) in DCM (10ml) was treated with trifluoroacetic acid (3ml) and stirred at room temperature for 3h, then concentrated under vacuum. The residue was dissolved in DCM and washed with 10% Na_2CO_3 solution, dried and concentrated under vacuum. The residue was purified by silica gel chromatography followed by trituration with Et_2O to afford the title compound as a pale brown solid (23mg, 61%). MH^+ 513.

Example 50

***cis*-1-[(2-Chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole (E50)**

A solution of E8 (1.8 g, 3.86 mmole) in DCM (150 ml) was treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (908 mg, 4.0 mmole) in DCM (50 ml) and the mixture stirred at room temp. under argon for 20 mins. The mixture was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4), and evaporated to a brown oil. Column chromatography on silica gel (eluent 5% MeOH/DCM) afforded the title compound as a yellow semi-solid (1.1 g, 61%), which was converted to its hydrochloride salt as a white solid.

^{1}H NMR (free base) (250MHz, $CDCl_3$) δ 8.06 (d, 1H), 7.72 (dd, 1H), 7.55 (d, 1H), 7.42 (m, 3H), 6.98 (dd, 1H), 6.61 (d, 1H), 4.45 (s, 2H), 3.49 (m, 2H), 2.59 (t, 2H), 2.40 (m, 2H), 2.31 (s, 3H), 1.15 (d, 6H). MH^+ 464/466.

Examples E51-E56 were prepared by a similar method to that of Example 50.

Example	MH^+
***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indole (E51)**	478
***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indole (E52)** (from E60)	461
***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylacetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole (E53)** (from E19)	533
***cis*-1-[(3-Chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole (E54)** (from E30)	430/432
***cis*-1-[(2,3-Dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole (E55)** (from E10)	446/448/449
***cis*-1-[(2-Fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indole (E56)** (from E32)	466

Example 57

***cis*-5-Methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E57)**

A stirred mixture of D13 (87mg, 0.33mmole), triethylamine (40mg, 0.40mmole) and diphenylphosphoryl azide (96mg, 0.35mmole) in toluene was heated at reflux under argon for 0.5h, then allowed to cool to room temperature and treated with a solution of D3 (70mg, 0.25mmole) in DCM (10ml). The mixture was stirred at room temperature for 4h, then treated with polystyrene bound trisamine (80mg of 3.6mmole/g) and polystyrene bound methylisocyanate (60mg of 1.2mmole/g) and stirred at room temperature for 70h, then filtered through Kieselguhr. The filtrate was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4), concentrated under vacuum and purified by chromatography on basic alumina eluting with EtOAc, followed by trituration with Et_2O to afford the title compound as a yellow solid (70mg, 52%).

^{1}H NMR (250MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.98 (d, 1H), 7.90 (d, 1H), 7.78-7.70 (m, 2H), 7.61 (d, 1H), 7.60-7.45 (m, 2H), 7.34 (d, 1H), 7.21 (d, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 4.25 (t, 2H), 3.85 (s, 3H), 3.38-3.21 (m, 4H), 2.67 (s, 3H), 2.55-2.40 (m, 4H), 2.30 (s, 3H), 1.09 (d, 6H). MH^+ 536.

Examples E58 - E65 were prepared by a similar method to that of Example 57 from indoline D3 or D37 and the appropriate carboxylic acid .consistent with the final product:

Example	MH^+
***cis*-5-Methoxy-1-[5-(6-methylpyridin-2-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E58)**	536
***cis*-5-Methoxy-1-[5-(2-methyloxazol-5-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E59)**	526
***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E60)**	463/465
***cis*-1-(3-Chloro-2-fluorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E61)**	447/449
***cis*-1-[3-Fluoro-2-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E62)**	481
***cis*-1-[2-Chloro-3-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E63)**	497/499
***cis*-1-[2-Chloro-3-methylphenyl)aminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E64)**	443/445
***cis*-1-[2-Chloro-3-(trifluoromethyl)phenyl)aminocarbonyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E65)**	481/483

Example 66

***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E66)**

A solution of D28 (10mg, 0.04mmole) in DCM (1ml) was treated with 2,3-dichlorophenyl isocyanate (10mg, 0.05mmole) and stirred at room temp for 16h. The mixture was applied to an SCX resin cartridge (500mg) and the resin eluted with DCM (x2), MeOH (x3) and the washings discarded. Final elution with 1M NH_3 in MeOH (x2) afforded the title compound as an off white solid (12mg, 69%). MH^+ 433/435.

Examples E67 - E72 were prepared by a similar method to that of Example 66 using indoline (D3, D30, D32 or D34) and the appropriate phenyl isocyanate consistent with the final product.

Example	MH^+
***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-5-chloro-6-(3,4,5-**	467/469

trimethylpiperazin-1-yl)indoline (E67)	
***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-5-bromo-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E68)**	513/515
***cis*-1-(2,3-Dichlorophenylaminocarbonyl)-5-ethyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E69)**	461/463
***cis*-5-Methoxy-1-[2-(trifluoromethyl)phenylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E70)**	433
***cis*-1-[2-Fluoro-3-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E71)**	480
***cis*-1-[2-Chloro-3-(trifluoromethyl)phenylaminocarbonyl]-3,3-dimethyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E72)**	525

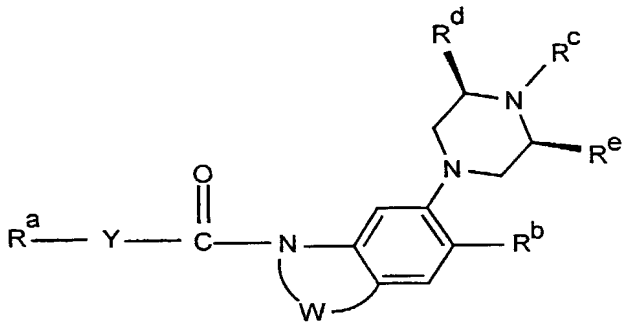
Example 73

***cis*-1-[(2-Chloro-3-trifluoromethyl)phenoxycarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (E73)**

Triphosgene (40mg, 0.13mmole) was added to a stirred solution of D3 (100mg, 0.36mmole) in DCM (10ml) which was maintained at room temperature for 1h, then treated with 2-chloro-3-(trifluoromethyl)phenol (78mg, 0.40mmole) and triethylamine (0.062ml, 0.44mmole). The mixture was heated under reflux for 4h, additional phenol (78mg) and triethylamine (0.062ml) added and heating continued for a further 8h. The mixture was washed with 10% K_2CO_3 solution, dried and concentrated under vacuum. The title compound was purified by chromatography on silica gel (84mg, 47%). MH^+ 498/500.

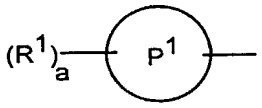
CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

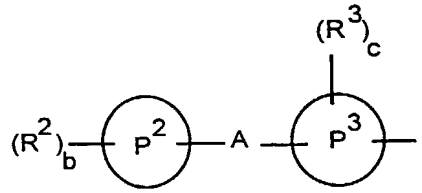
in which R^a is a group of formula (i)



(i)

wherein P^1 is phenyl, naphthyl or heteroaryl;
R^1 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, nitro, CF_3, cyano, SR^6, SOR^6, SO_2R^6, $SO_2NR^6R^7$, CO_2R^6, $CONR^6R^7$, $OCONR^6R^7$, NR^6R^7, $NR^6CO_2R^7$, $NR^6CONR^7R^8$, $CR^6{=}NOR^7$ where R^6, R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;
a is 0, 1, 2 or 3;

or R^a is a group of formula (ii)



(ii)

wherein
P^2 is phenyl, naphthyl, heteroaryl or a 5 to 7 membered heterocyclic ring;
P^3 is phenyl, naphthyl or heteroaryl;
A is a bond or oxygen, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;

R^2 is as defined above for R^1 in formula (i) or R^2 is heteroaryl optionally substituted by C_{1-6}alkyl, halogen or COC_{1-6}alkyl or is a 5 - 7 membered heterocyclic ring optionally substituted by oxo;
R^3 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, hydroxy, nitro, CF_3, cyano, CO_2R^6, $CONR^6R^7$, NR^6R^7 where R^6 and R^7 are as defined above;
b and c are independently 0, 1, 2 or 3;

Y is a single bond, CH_2, O or NR^5 where R^5 is hydrogen or C_{1-6}alkyl;
W is $-(CR^9R^{10})_t-$ where t is 2, 3 or 4 and R^9 and R^{10} are independently hydrogen or C_{1-6}alkyl or W is a group -CH=CH-;
R^b is hydrogen, halogen, hydroxy, C_{1-6}alkyl, CF_3 , COC_{1-6}alkyl, cyano or C_{1-6}alkoxy;
R^c is hydrogen or C_{1-6}alkyl;
R^d and R^e are independently C_{1-4}alkyl.

2. A compound according to claim 1 in which R^a is a group of formula (i) wherein P^1 is phenyl.

3. A compound according to claim 2 in which R^1 is halogen, C_{1-6}alkyl, nitro, CF_3 or cyano.

4. A compound according to any of the preceding claims in which Y is CH_2.

5. A compound according to claim 1 in which R^a is a group of formula (ii) wherein A is a single bond, P^3 is phenyl or naphthyl and P^2 is phenyl, pyridyl, pyrazinyl, oxadiazolyl, oxazolyl or piperidinyl.

6. A compound according to any of the preceding claim in which W is $-CH_2-CH_2-$ or -CH=CH-.

7. A compound according to any of the preceding claims in which R^c is hydrogen or methyl.

8. A compound according to any of the preceding claims in which R^d and R^e are both methyl.

9. A compound according to claim 1 which is a compound E1 - E73 (as described above) or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 which is

cis-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole,
cis-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline,
cis-1-[(2,3-dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline
cis-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl]-indoline,
cis-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole,
cis-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indole,
cis-1-[2-chloro-3-(trifluoromethyl)phenyl)aminocarbonyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline
or a pharmaceutically acceptable salt thereof.

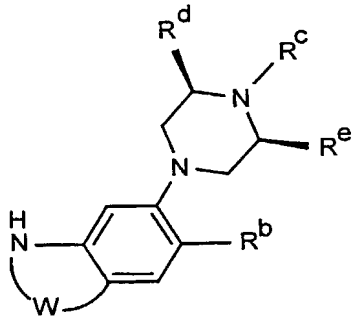
11. A process for the preparation of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof which comprises:

(a) where Y is NH, coupling a compound of formula (II):

$$R^a\text{–N-(C = O)}$$

(II)

in which R^a is as defined in formula (I) with a compound of formula (III):



(III)

in which W, R^b, R^c, R^d and R^e are as defined in formula (I); or

(b) where Y is NR^5, reacting a compound of formula (IV)

$$R^a\text{-}NR^5H$$

(IV)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) as defined above together with an appropriate urea forming agent; or

(c) where Y is a single bond, CH_2 or O, reacting a compound of formula (V)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L$$
(V)

in which R^a is as defined in formula (I) and L is an appropriate leaving group, with a compound of formula (III) as defined above;
and optionally thereafter for process (a), (b) or (c):

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

12. A compound according to any one of claims 1 to 10 for use in therapy.

13. A compound according to any one of claims 1 to 10 for use in the treatment of depression.

14. A pharmaceutical composition which comprises a compound according to any of claims 1 to 10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

15. A compound of formula (I) as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT_{1B} receptor is beneficial.

16. The use of a compound of formula (I) as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT_{1B} receptor is beneficial.

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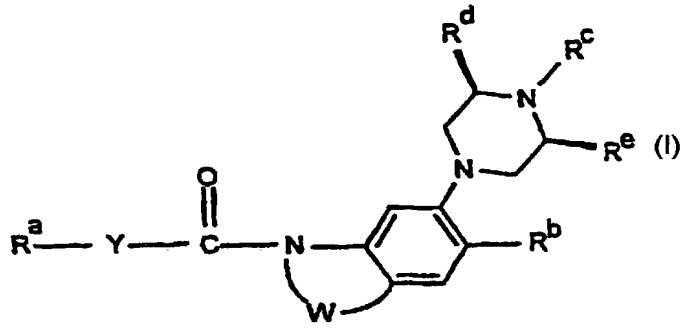
(54) Title: PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS



(57) Abstract: Piperazine derivatives of formula (I) processes for their preparation, pharmaceutical compositions containing them and to their use in therapy as 5-HT_{1B} antagonists. W,Y,R^a-$R^e$are so defined in the application.

WO 01/23374 A1

Docket No.: P32422 PCT/EP00/09442

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PIPERAZINE DERIVATIVES AS 5-HT1B ANTAGONISTS

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on 21 September 2000 as Serial No. PCT/EP00/09442
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9922831.4	GREAT BRITAIN	25 SEPTEMBER 1999	Yes
0001936.4	GREAT BRITAIN	27 JANUARY 2000	Yes
0013873.5	GREAT BRITAIN	7 JUNE 2000	

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No. Filing Date Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

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